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REVIEW

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Lymphopenia in sepsis: a narrative review

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Abstract

This narrative review provides an overview of the evolving significance of lymphopenia in sepsis, emphasizing its critical function in this complex and heterogeneous disease. We describe the causal relationship of lymphopenia with clinical outcomes, sustained immunosuppression, and its correlation with sepsis prediction markers and therapeutic targets. The primary mechanisms of septic lymphopenia are highlighted. In addition, the paper summarizes various attempts to treat lymphopenia and highlights the practical significance of promoting lymphocyte proliferation as the next research direction.

Keywords Sepsis, Lymphopenia, Mechanism, Immunotherapy

Graphical Abstract

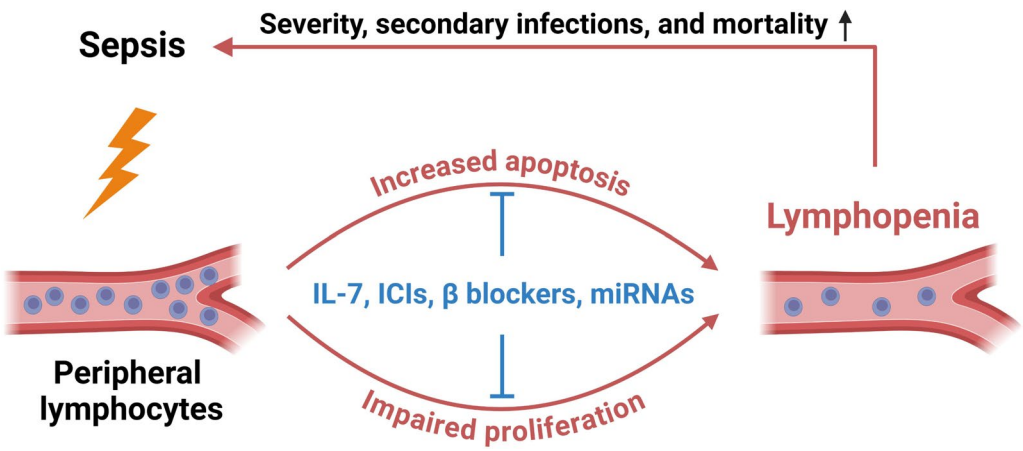

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Table 1 Established knowledge and unanswered questions about sepsis-induced lymphopenia

Established knowledge	Unanswered questions
Definition and Prevalence: Lymphopenia, characterized by reduced lymphocyte counts, commonly occurs in sepsis and impacts many patients [5, 11, 12].	*Heterogeneity*: Different patients experience lymphopenia during sepsis differently, and the factors contributing to this heterogeneity are not fully understood.
Role in Immune Dysfunction: Lymphopenia in sepsis contributes to impaired immune responses, thereby increasing vulnerability to secondary infections and adversely impacting patients' recovery, but also persists for an extended period post-sepsis, leading to long-term immunosuppression [13–15].	*Intervention Strategies*: Elucidating the specific contribution of sepsis-induced lymphopenia to immune paralysis and its long-term effects on immunological memory and susceptibility to future infections is essential for developing precision therapies.
Mechanism: A primary mechanism of lymphopenia in sepsis is the apoptosis of lymphocytes, a process exacerbated by the systemic inflammatory response typical in sepsis [16–19].	*Mechanisms Beyond Apoptosis*: While apoptosis is a known cause of lymphopenia, other underlying mechanisms, particularly those involved in restoring lymphocyte counts, remain to be fully elucidated.
Impact on Specific Lymphocyte Subtypes: Sepsis-induced lymphopenia affects all major lymphocyte subtypes, including T cells, B cells, and NK cells, although the degree and impact can vary among these subtypes [18, 20–22].	*Patient Stratification for Tailored Treatment*: Developing strategies for patient stratification based on the degree and characteristics of lymphopenia in sepsis can optimize personalized treatment approaches.
Correlation with Sepsis Severity and Mortality: The degree of lymphopenia in septic patients correlates with the severity of sepsis, and more severe lymphopenia is linked to worse clinical outcomes and even higher mortality rates [5, 7, 12, 23].	*Thresholds for sepsis-induced lymphopenia*: Determining the threshold (or duration) of lymphopenia and the degree of reduction in the number (or proportion) of lymphocyte subpopulations remains unclear.
Therapeutic Challenges: Addressing lymphopenia in sepsis presents therapeutic challenges, as interventions must balance restoring immune function without exacerbating harmful inflammation [24–26].	*Optimal Therapeutic Strategies*: Determining the most effective therapeutic approaches to counter lymphopenia in sepsis, including timing, type, and dosage of drug intervention, remains a significant challenge.

Background

Sepsis, a life-threatening condition that arises when the body's response to infection damages host tissues and organs, imposes a substantial global pathological burden [1]. Recent estimates suggest that sepsis affects nearly 50 million people worldwide each year, leading to high mortality rates and huge healthcare costs [2]. Despite substantial advances in medical science, sepsis continues to represent a significant public health challenge, necessitating innovative strategies to mitigate its global impact.

Lymphopenia, alternatively termed lymphocytopenia, delineates a pathological state characterized by a diminished concentration of lymphocytes in the peripheral blood [3]. The etiology of lymphopenia encompasses a range of factors, including infections, autoimmune disorders, pharmacological interventions, and exposure to radiation therapy [3]. The relationship between lymphopenia and sepsis has been extensively studied, and in particular, sepsis-induced lymphopenia is gradually being recognized as an essential factor in the prognosis of sepsis [4]. Sepsis-induced lymphopenia is usually defined as an absolute lymphocyte count (ALC) of less than 1,000 cells/μL [5–7]. Several studies have also provided individualized threshold data, e.g., the persistence with the lymphopenia cut-off value (<760cells/μL$)>3$ days in non-viral infection-related sepsis indicates a higher 28-day mortality rate [8], and severe lymphopenia in sepsis was previously defined as an ALC of less than 500/μL [9]. However, despite the significant progress in this field, numerous unresolved issues still require urgent attention (Table 1). In addition, altering myeloid cell numbers during sepsis is a relatively complex and diverse process. This issue has been discussed by others [10] and is beyond the scope of this review.

Notably, sepsis-induced lymphopenia has been associated with worse outcomes, including increased risk of secondary infections, multiple organ failure, and death [7, 23]. Given the widespread role of lymphopenia in sepsis, there is a growing recognition of the potential practical significance of treatments that address lymphopenia [27–30]. The main controversies and challenges faced by the medical community in addressing these questions include the complexity of the immune response in sepsis, the difficulty of distinguishing cause and effect in observational studies, and the lack of specific treatments. Moreover, the emergence of the COVID-19 pandemic has further complicated the scenario, resulting in an increased incidence of sepsis cases. This rise is coupled with the pandemic's tendency to cause lymphopenia, which merits additional investigation to unravel the intricate pathophysiological pathways in sepsis [15].

In conclusion, the global pathological burden of sepsis is profound and necessitates innovative strategies for mitigation. In this light, the present review aims to explore and synthesize the current knowledge regarding lymphopenia in sepsis, focusing on its mechanisms, clinical implications, and potential therapeutic interventions. By critically analyzing recent findings, this review seeks to identify gaps in our current understanding and develop more effective management strategies for sepsis.

Timeline of lymphopenia in sepsis

Before the 1970s, research on sepsis, including lymphopenia, was in its early stages, focusing more on clinical identification than immunological mechanisms. The early 1900s saw sepsis recognized as a severe condition with a limited understanding of its pathophysiology. The 1930s brought advances in microbiology, crucial for later insights into sepsis-related immune responses, including lymphocyte depletion. In the 1950s, antibiotics improved sepsis treatment, but knowledge of the immune system's role, particularly regarding lymphopenia, continued to develop.

In the 1970s, a significant correlation was found between preoperative lymphocyte counts and sepsis risk by assessing six postoperative sepsis risk factors in 105 gastrointestinal surgery patients [31]. A similar prospective investigation of the same risk factors was conducted in an additional 125 patients undergoing major surgery, with similar results [31]. Preoperative lymphocyte counts were a simple and reliable measure of host resistance. The first international definition of sepsis had yet to be formed. However, people had begun to realize that the decreased lymphocyte counts were related to the reduced host resistance caused by wound infection.

In the 1990s, a characteristic lymphocyte phenotype was reported in 105 severely injured trauma patients throughout their hospital stay. A significant reduction in lymphocytes occurred during the first week after injury, with the lowest numbers of helper T cells and suppressor cells found in the deceased population [32]. Reconstitution of these subpopulations may reduce the risk of infection. On the first day after major abdominal and chest surgery, all lymphocyte subpopulations fell synchronously to less than 50% of the reference range (CD3 + to < 600/μL, CD4 + to < 400/μL and CD8 + to < 250/μL), which predicted the occurrence of postoperative infections with an accuracy of 89%, a sensitivity of 80%, and a specificity of 96% [33]. At this stage, researchers introduced the lymphocyte apoptosis concept into lymphopenia by inducing apoptosis in lymphatic and non-lymphatic organs through cecum ligation and puncture (CLP) operation in mice [34]. They subsequently found that blocking lymphocyte apoptosis improved survival in sepsis [35, 36].

At the beginning of this century, Multiple studies have repeatedly observed a significant decrease in circulating lymphocyte count [21, 37–41]. In 2009, a study found that homeostatic control in the sepsis environment restored T-cell pools to normal levels without generating antigen-specific memory or abnormal T-cell specificity [42]. In 2013, sepsis-induced immune suppression was identified as a result of cell dysfunction, and the mainstream view is that lymphopenia remains an essential factor in the progression of sepsis [43]. In 2014, persistent lymphopenia after sepsis diagnosis was reported to be predictive of mortality [6]. In 2016, the latest international consensus on sepsis (sepsis 3.0) was released, with a redefined standard for sepsis that better reflects organ dysfunction and response dysregulation [44]. In 2017, apoptosis-induced lymphopenia was re-emphasized as a frequent process during sepsis and severe injuries (e.g., burns, major surgery, and trauma) [16]. Subsequently, lymphopenic community-acquired pneumonia (L-CAP)

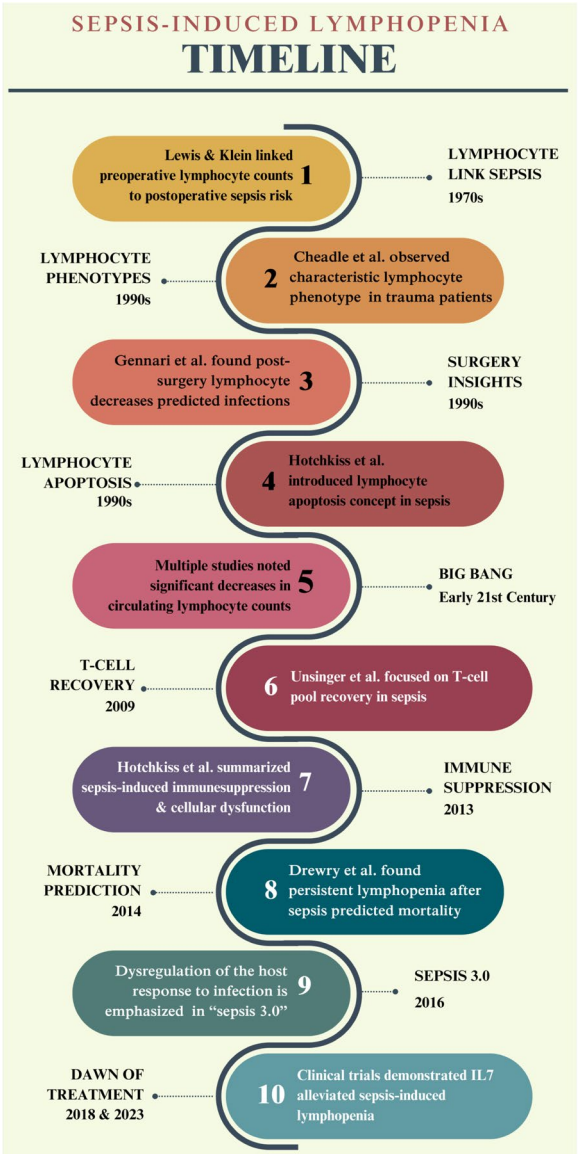
SEPSIS-INDUCED LYMPHOPENIA
TIMELINE
Lewis & Klein linked preoperative lymphocyte counts to postoperative sepsis risk 1
LYMPHOCYTE LINK SEPSIS 1970s
LYMPHOCYTE PHENOTYPES 1990s
2 Cheadle et al. observed characteristic lymphocyte phenotype in trauma patients
Gennari et al. found post-surgery lymphocyte decreases predicted infections 3
SURGERY INSIGHTS 1990s
LYMPHOCYTE APOPTOSIS 1990s
4 Hotchkiss et al. introduced lymphocyte apoptosis concept in sepsis
Multiple studies noted significant decreases in circulating lymphocyte counts 5
BIG BANG Early 21st Century
T-CELL RECOVERY 2009
6 Unsinger et al. focused on T-cell pool recovery in sepsis
Hotchkiss et al. summarized sepsis-induced immunesuppression & cellular dysfunction 7
IMMUNE SUPPRESSION 2013
MORTALITY PREDICTION 2014
8 Drewry et al. found persistent lymphopenia after sepsis predicted mortality
Dysregulation of the host response to infection is emphasized in "sepsis 3.0" 9
SEPSIS 3.0 2016
DAWN OF TREATMENT 2018 & 2023
10 Clinical trials demonstrated IL7 alleviated sepsis-induced lymphopenia

Fig. 1 Timeline of sepsis-induced lymphopenia. Half a century of research on the relevance and pathophysiology of lymphopenia to sepsis suggests the promise of therapeutic strategies targeting lymphopenia in sepsis immunomodulation

[45] and lymphopenic hospital-acquired sepsis [7] were identified as an immunophenotype with a higher risk of death. In 2019, lymphopenia was found to be independently associated with a higher 28-day mortality rate in patients with sepsis [46]. During the same period, lymphopenia was also identified as a standalone indicator of 90-day mortality in patients with acquired immune dysfunction pneumonia in the intensive care unit (ICU) [47]. These evidences imply that lymphopenia is reliable for forecasting short-term and long-term patient outcomes. In 2020, two studies of COVID-19 patients found severe lymphopenia in these patients [48, 49]. Recently, two randomized controlled double-blind trials in patients with septic shock and severe lymphopenia demonstrated that IL-7 reversed sepsis-induced lymphopenia and increased T-cell proliferation and activation [28, 29].

After more than 50 years, the relationship between lymphopenia and sepsis-associated immunosuppression and its phenotypic, mechanistic, and therapeutic studies suggest the value and promise of therapeutic strategies targeting lymphopenia in treating sepsis (Fig. 1). Further investigation of the pathophysiological process of sepsis-associated lymphopenia and searching for new precise treatments is crucial for the immunomodulation of sepsis.

Role of lymphopenia in the progression and outcome of sepsis

Association with sepsis progression

Although lymphocyte count reduction, routinely defined as less than 1 to 1.5×10^9/L, is commonly encountered in clinical monitoring, it is seldom utilized as a diagnostic criterion for ICU admissions. However, early studies have underscored its clinical utility in the urgent diagnosis of bacteremia patients and in predicting postoperative sepsis [31, 50, 51]. Statistics indicate that 74% of septic patients experienced a decline in lymphocyte count (below 1.5×10^9/L) within the first 1–2 days, and 56% had not returned to a normal lymphocyte count by days 6–8 [52].

According to a study conducted in China, severe sepsis patients exhibited a lower lymphocyte count (0.8×10^9/L, Q_L=0.50, Q_u=1.12) in comparison to the low-risk group (lymphocyte count of 0.9×10^9/L, Q_L=0.65, Q_u=1.42) [53]. Another research highlighted significant disparities in the median lymphocyte counts between sepsis patients, critically ill non-sepsis patients, and healthy control groups, registering at 0.9×10^9/L, 1.1×10^9/L, and 1.8×10^9/L respectively, with the interquartile ranges being 0.6–1.3, 0.7–1.6, and 1.4–2.3×10^9/L [54]. A large-scale European study corroborated that a lymphocyte count < 1.1×10^9/L correlated with a heightened multi-variable adjusted risk ratio of 1.51 (95% CI 1.21–1.89) for sepsis diagnosis, aligning with increased risks of hospital infections and infection-related mortality [55].

In a retrospective study that included 77 sepsis and 23 non-sepsis adult patients, the daily lymphocyte count of the patients was calculated until discharge or death [8]. Lymphocytes exhibited a high diagnosis of sepsis with an area under the curve value of 0.971 (95% CI = 0.916–0.994). The diagnostic efficacy of lymphocytes was more significant than other biomarkers, such as white blood cells, neutrophil count, and procalcitonin. The results also showed that the 28-day mortality rate was 39.66% in patients with persistent lymphocyte counts below 0.76×10^9/L, significantly higher than in patients without persistent lymphopenia. ALC is a promising, low-cost, rapid, and readily available biomarker for diagnosing sepsis. High vigilance is required for sepsis when a non-viral infection is suspected and lymphopenia levels are below the optimal threshold (0.76×10^9/L) value. In another single-center retrospective cohort study of 335 adult patients with bacteremia and sepsis, complete blood cell counts were recorded for the first four days following the diagnosis of sepsis [6]. On Day 4, the median ALC was significantly higher in survivors than in non-survivors (1.1×10^3 cells/μl [IQR 0.7, 1.5] vs. 0.7×10^3 cells/μl [IQR 0.5, 1.0]). ALC was also found to be independently associated with 28-day survival (adjusted OR 0.68 [95% CI 0.51, 0.91]) and 1-year survival (adjusted OR 0.74 [95% CI 0.59, 0.93]). Thus, persistent lymphopenia on the fourth day after sepsis diagnosis predicts early and late mortality and may serve as a biomarker for sepsis-induced immunosuppression.

It should be noted that some studies demonstrated no significant correlation between persistent lymphopenia and the incidence of hospital-acquired infections in critically ill patients [56]. Conversely, the neutrophil-to-lymphocyte count ratio [57, 58] and the IL-10-to-lymphocyte count ratio [59] offer a more reliable reflection of the severity of sepsis. Additionally, investigations into subpopulations of lymphocytes have furnished valuable insights, wherein specific subsets of T and B lymphocytes displayed variations associated with the gravity of sepsis [60–62]. For instance, CD3 + T lymphocyte counts manifested a decreasing trend in patients with early clinical deterioration (0.5×10^9/L ± 0.5 versus 0.7×10^9/L ± 0.5, p = 0.06) [61]. Although changes in B cells were not as pronounced as those in T cells, there was a significant reduction in CD19 + CD23 + B cells at admission in septic shock patients, followed by a marked augmentation in survivors, implying these cells potentially harbor significant prognostic value [62].

Impact on mortality

Numerous studies have affirmed a significant correlation between the degree of lymphopenia within 28 days and the incidence of hospital-acquired infections and mortality [6, 9, 38, 40, 41, 63]. There is a link between the failure to normalize lymphocyte levels post-trauma and higher mortality [63]. In parallel, a sustained decline in lymphocyte levels after sepsis diagnosis, mainly due to T-cell reduction, is associated with increased mortality [6]. In septic patients, a notable reduction in γδ T-cell numbers in the intestinal mucosa compared to healthy controls is linked to increased disease severity and higher mortality rates [19]. A recent study revealed that children with severe sepsis and persistent lymphopenia face higher risks of multi-organ dysfunction syndrome or death in pediatric intensive care units, with the lymphopenia persisting as a composite outcome odds ratio of 2.98 (95% CI [1.85–4.02]; $p < 0.01$) [5]. Specific research further delineates that a severe T-cell reduction can only serve as a prognostic marker for immune suppression when accompanied by a high proportion of circulating immature granulocytes, attributable to the enhanced T-cell apoptosis mediated by MDSC present in immature granulocytes [6, 64, 65].

Lymphopenia is also hypothesized to be a potential cause or consequence of CAP, potentially associated with chronic illnesses, critical illnesses, lymphocyte adherence to vascular endothelium, or extensive migration to the lungs [45]. A lymphocyte count below 1,000/μL may be an independent biomarker for a 30-day mortality rate in CAP patients. For patients in the L-CAP study, a lymphocyte count under 724/mm³ doubled the risk of in-hospital death within 30 days [45]. Therefore, lymphopenia markedly correlates with higher ICU admission risks and in-hospital and 30-day mortality rates in CAP patients compounded with sepsis. Early identification of lymphopenia may facilitate pinpointing CAP septic patients who are in urgent or impending need of intensive care [7]. A significant correlation was observed between a lymphocyte count below the usual lower limit and the mortality rate in a study involving 3099 COVID-19 patients. Specifically, the lymphocyte count was exceedingly low (less than 5% of white blood cells) in deceased individuals. In contrast, it remained within normal ranges (more than 20% of white blood cells) in survivors with moderate illness [11].

L-CAP is characterized by CD4 depletion, a higher inflammatory response, and low IgG2 levels that correlate with greater severity at presentation and worse prognosis [66]. Earlier, both reduced T-lymphocyte counts and reduced IgG levels were reported to be associated with the poor prognosis of severe CAP [67]. In addition, the researchers also found that the severity of CAP was associated with decreased serum immunoglobulin levels (including total IgG, IgG1, and IgG2) and that low levels of immunoglobulins were independently associated with ICU admission and 30-day mortality [68]. Lymphopenia leading to reduced immunoglobulin levels is predictable. A recent study found that TNF-α was significantly lower in gradable lymphopenia compared to non-lymphopenia and that a lower TNF-α baseline may lead to a reduced number of B-cells and immature B-cells, which can result in lower immunoglobulin levels [69]. Immunoglobulin deficiency is also an indicator of severity in COVID-19 patients, and i.v. administration of IgG can mitigate virus-induced immunosuppression and provide passive immune protection against a broad range of pathogens [70].

The results of the above studies collectively show that lymphopenia is strongly associated with higher mortality rates, substantiating its role as a predictive biomarker and potential therapeutic target for critically ill patients [71]. Notably, in studies significantly correlated with the probability of death on day 28, over 30% of patients exhibited lymphopenia, correlated with aggravated prognosis associated with profound T-cell lymphopenia [61].

Relation with secondary infections

The reduction in T lymphocytes holds predictive value for higher risks of secondary infections and prolonged hospital stays [40, 61, 72, 73]. Lymphopenia is closely associated with secondary infections and complications, including infections in the lungs, urinary tract, bloodstream, and abdomen [6]. Distinct from the intrinsic functional status of individual T cells, the heightened susceptibility to secondary infections due to lymphopenia mainly manifests through extensive adaptive cell apoptosis, reduced T-cell diversity [74], and an immune suppression state induced by the relative increase in suppressive cells. The diversity of T-cell receptors (TCR) is critical to ensuring an individual's effective immune responses to various foreign antigens in a fluctuating environment. Research indicates that the loss of TCR diversity is induced by a reduction in lymphocytes, which aligns with the study outcomes showing a decrease in the proportion of Naïve T cells rather than a reduction in memory T cells [21, 39, 75].

Consequently, the discussion on the decline in lymphocytes continues to encompass the loss of TCR diversity, particularly from thymic atrophy caused by cellular apoptosis. It has been discovered that there is a notable decline in TCRβ diversity in adult patients with sepsis, correlating with an increased mortality rate [76, 77]. In the context of long-term use of invasive devices such as intubation, catheterization, and central venous catheterization, reduced TCR diversity could potentially heighten

Table 2 Sepsis-induced lymphopenia with secondary infections and outcome

Relevance	Observations	References
Disease progress	Lymphocyte counts were lower in patients with severe sepsis compared to low-risk patients.	[53]
	Patients with sepsis have significantly lower lymphocyte counts compared to non-septic critically ill patients and healthy controls.	[54]
	CD3 + T lymphocyte counts manifested a decreasing trend in patients with early clinical deterioration.	[61]
Mortality	There is a link between failure to normalize lymphocyte counts post-trauma and higher mortality.	[63]
	A sustained decrease in lymphocyte counts after the diagnosis of sepsis (mainly due to T-cell reduction) is associated with increased mortality.	[6]
	The marked reduction in the number of γδ T cells in the intestinal mucosa of septic patients is associated with increased mortality.	[19]
	Children with severe sepsis and persistent lymphopenia face a higher risk of MODS or death.	[5]
	Lymphocyte counts below 1,000/μL can be used as an independent biomarker of 30-day mortality in CAP patients.	[45]
Secondary infections	Lymphopenia is closely associated with secondary infections and complications, including infections in the lungs, urinary tract, bloodstream, and abdomen.	[6]
	Reduced TCR diversity due to septic lymphopenia increases susceptibility to hospital-acquired infections associated with certain chronic viral infections (e.g., hepatitis C virus).	[39, 78]
	Lymphopenia causes sepsis patients to be unable to thoroughly eliminate high pathogen loads, facilitating the reactivation of viruses carried in the body.	[54]

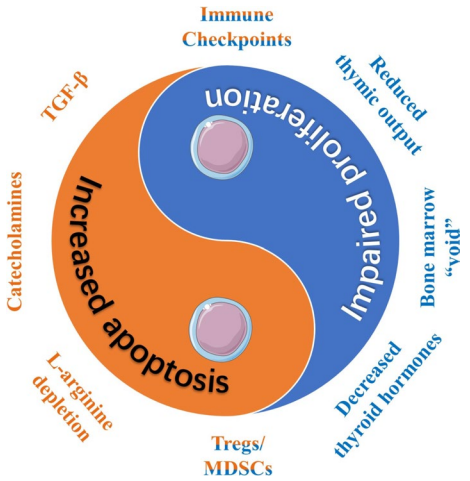

Fig. 2 Increased apoptosis and impaired proliferation of lymphocytes contribute to sepsis-induced lymphopenia. TGF-β and catecholamine release or L-arginine depletion during sepsis enhance lymphocyte apoptosis. Reduced thymic output, bone marrow "void", or decreased levels of thyroid hormones limit the effective proliferation of lymphocytes after the onset of septic lymphopenia. Immune checkpoints and inhibitory cells, including regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), induce apoptosis and impair proliferation

susceptibility to hospital infections related to certain chronic viral infections (e.g., hepatitis C virus), which are more prone to immune evasion [39, 78]. In addition, 42.7% of sepsis patients harbor multiple viruses [54], considering the cellular exhaustion, reduced CD4 and CD8 T cells, and increased myeloid-derived suppressor cells and regulatory T cells, all of which could facilitate viral reactivation due to the inability to eliminate high pathogen loads thoroughly. The association between lymphopenia and the progression and outcome of sepsis is summarized in Table 2.

Mechanism of sepsis-induced lymphopenia

Immune system homeostasis depends on the balance between immune cell proliferation and death. In sepsis-associated immune disorders, a persistent decrease in absolute lymphocyte counts is essential for assessing immunosuppression and poor prognosis [79]. The lymphocyte population undergoes apoptosis upon the onset of sepsis, significantly reducing the number of B cells and CD4 + and CD8 + T cells [71]. Meanwhile, peripheral blood lymphocyte counts in ICU survivors began to rebound within 72 h after admission to the ICU [32]. Lymphocyte counts in surviving septic mice returned to normal levels at approximately three weeks post-infection [42]. Thus, the homeostasis of lymphocyte counts in the septic host undergoes a biphasic process of disruption and repair. Lymphocytes undergo a predominantly apoptotic "loss", while multiple factors regulate their expansion capacity. Patients with sepsis whose lymphocyte counts are not effectively restored may experience excessive apoptosis and proliferative dysfunction of lymphocytes (Fig. 2).

Lymphocyte apoptosis

Apoptosis is pivotal in reducing lymphocytes, as corroborated by several comprehensive studies [76, 80]. The T

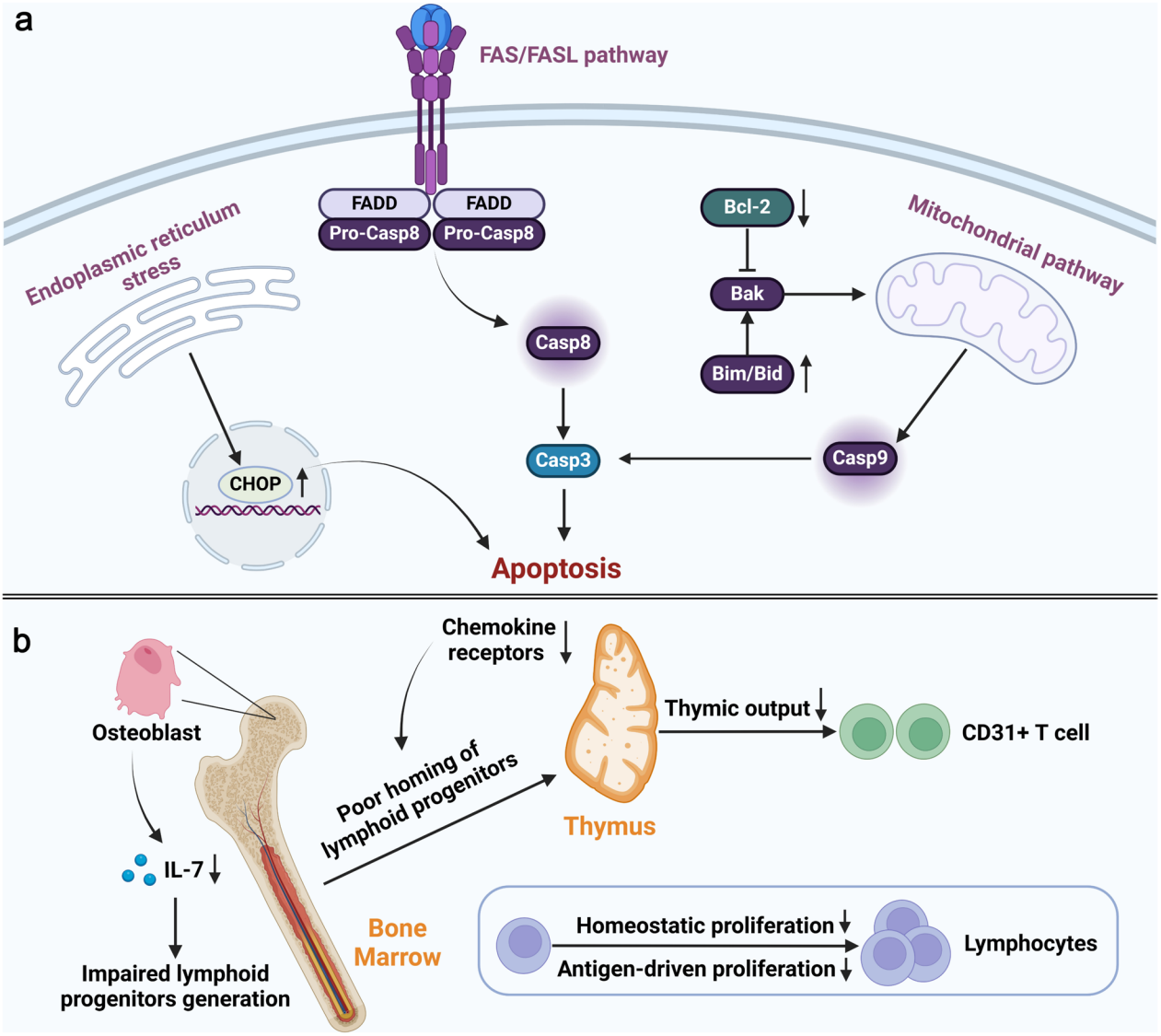

Fig. 3 Cellular and molecular mechanisms of sepsis-induced lymphopenia. **a** Fas/FasL pathway, mitochondrial pathway, and endoplasmic reticulum stress-mediated apoptosis are all involved in sepsis-induced apoptosis of lymphocytes. **b** Reduced thymic output, impaired lymphoid progenitor cell generation, poor thymic homing, and insufficient peripheral homeostatic or antigen-driven proliferation combine to diminish lymphocyte proliferative capacity after sepsis

lymphocytes' abnormal activation (either hyperactivation or suppression) is closely associated with alterations in subpopulation differentiation, predominantly influenced by their apoptotic regulatory mechanisms [19, 81]. The Fas/FasL pathway, the mitochondrial pathway, and the endoplasmic reticulum stress (ERS)-mediated apoptosis are both involved in extensive lymphocyte apoptosis (Fig. 3a) [82, 83]. The activation of Caspase family proteases is involved in the terminal execution field of lymphocyte apoptosis [84, 85].

The Fas/FasL signaling pathway mediates lymphocyte apoptosis in organ tissues [86, 87] and significantly contributes to apoptotic damage. Activated T cells highly express Fas receptors, especially cytotoxic T lymphocytes strongly activated by antigen; after killing Fas-expressing target cells, they also kill their Fas-expressing companions. In addition, soluble FasL shed on the cell membrane kills its cells or neighboring activated T cells in an autocrine and paracrine manner, referred to as reactivation-induced cell death (RICD) [88]. RICD is induced by an exogenous signaling transduction pathway through the caspase-8, which triggers the downstream executor caspase-3 [89]. Notably, mouse and human CD4+T cells show differences in sensitivity to Fas-mediated RICD [90,

91]. In contrast, human CD8 + T cells are more sensitive to TNF receptor 1-mediated RICD [92], and the reasons for this warrant further exploration.

Sepsis-induced apoptosis in thymocytes and splenocytes cannot be blocked entirely in Fas receptor or TNF-p55 or TNF-p75 receptor-deficient mice [18, 93], suggesting the existence of other forms of apoptotic pathways. The mitochondrial enzyme activity of T cells in the peripheral blood of septic patients is significantly reduced compared with that of healthy controls [94]. Caspase-9 is a crucial downstream link in the mitochondrial apoptotic pathway, and nonsurvivors of sepsis show positive expression of cleaved caspase-9 in splenic T cells [18]. Besides, the Bcl-2 protein can block thymic and splenic T cell apoptosis by inhibiting the mitochondrial pathway but not the death receptor pathway [35]. Intracellular regulation encompasses the upregulation of pro-apoptotic genes, including Bim, Bid, and Bak, coupled with the downregulation of anti-apoptotic gene Bcl-2 expression [82].

The unfolded protein response (UPR) is usually activated to counteract lymphocyte stress. However, with the progression of sepsis, when the UPR fails to maintain cellular homeostasis, the ERS response is transformed into a pro-apoptotic response, with up-regulation of the critical nuclear transcription factor, C/EBP homologous protein (CHOP), driving apoptosis in splenocytes [83]. In addition, the expression of stimulator of interferon genes (STING) can also lead to apoptosis by triggering ERS in splenic T-cells [95]. In contrast, the Notch intracellular segment can block STING-mediated apoptosis by competing with cyclic guanosine monophosphate-adenosine monophosphate for cyclic dinucleotide binding sites on STING [96].

Extracellular regulation principally involves inflammatory cytokines that partake in the upstream regulatory processes of lymphocyte apoptosis, wherein TGF-β1 may induce lymphopenia through modulating pro-apoptotic pathways [97]. During the septicemic phase, another pronounced characteristic is the sustained and exacerbated activation of the sympathetic nervous system, chiefly manifested as the excessive release of endogenous catecholamines [98]. Catecholamine substances, including dopamine and dobutamine, can foster lymphocyte apoptosis by impacting β receptors on the cell surface [99].

Cell fate after trauma and sepsis may depend on autophagy and apoptosis crosstalk [100]. In a mouse model of CLP, apoptosis of splenic T cells occurs along with reduced levels of autophagy in CD4 + and CD8 + T cells [101, 102]. In addition, mice with lymphocyte-specific knockout of Atg5 or Atg7 showed significantly increased mortality, immune dysfunction, and T-cell apoptosis after CLP [101, 102], and deletion of Atg5 resulted in enhanced levels of the anti-inflammatory cytokine IL-10 after CLP, suggesting that autophagy deficiency is involved in septic immunosuppression.

Other mechanisms of cell death may also be involved in lymphopenia. Necroptosis occurred in T cells lacking caspase-8 on the TNF receptor signaling pathway, suggesting that necrotic apoptosis can be substituted for apoptosis when some factor leads to the failure of apoptotic mechanisms in T cells [103]. Antigen-specific CD4 + and CD8 + T cells lacking glutathione peroxidase four fail to expand, and the T cells rapidly accumulate membrane lipid peroxides with subsequent ferroptosis [104]. Follicular helper T cells are uniquely sensitive to caspase-dependent cellular pyroptosis due to the response to ATP by the ionotropic ATP-gated receptor P2X7 [105, 106]. T-cell pyroptosis can be induced by caspase recruitment domain-containing protein 8 in the resting state. However, pyroptosis is inhibited in the TCR-activated state, suggesting that activation of first signals blocks initial T-cell pyroptosis [107, 108]. Although direct evidence for the above forms of cell death and T-cell loss after sepsis is lacking, it suggests that there may be a more complex regulatory mechanism behind T-cell death in sepsis.

Supplementary obstacle

Following a rapid decrease over 1–2 days, the T cell counts in the majority of survivors initiate recovery between days 4 and 7 [61, 66, 77], with CD4 + T cells being the principal contributors [17, 18, 40, 42, 109–111]. A poor prognosis is generally observed in patients unable to reach a significant T cell count recovery within this period. Notably, the CD4 + count in survivors nearly doubled from day 1 to day 4, a trend similarly noted in the recovery of CD8 + T cells. This dynamic of T lymphocyte quantity alterations also mirrors observations noted in sepsis mouse models, where a drastic decline in secondary lymphoid tissue cell numbers on day three post-induction was followed by a swift recovery, exceeding control group levels by day 8 [112]. Although lymphocyte numbers can be progressively restored during sepsis, the proliferation mode needs to be better defined. It may originate from three scenarios: thymic output, bone marrow regeneration, and homeostatic or antigen-driven proliferation (Fig. 3b). Maintenance of peripheral T lymphocyte counts relies on thymic development and out-migration of mature T-cells. Typically, lymphopenia induces non-antigen-dependent homeostatic proliferation [113].

The thymus is the primary source of naive T lymphocytes. However, the numbers of total lymphocytes, double-positive cells, single-positive cells, and double-negative cells are significantly reduced in sepsis [42, 114].

The thymocyte counts in the sepsis model decreased significantly as early as 3 h post-induction and hit a nadir on day 3 [115]. The reduction in thymic output is directly confirmed by a decrease in the relative number of CD31 + thymus emigrating cells and an increase in the relative number of CD31- T cells (a characteristic of peripherally expanded initial T cells) in the peripheral blood of septic mice [14]. The main mechanisms by which sepsis induces impaired thymic lymph angiogenesis include poor homing of lymphoid progenitors from the bone marrow to the thymus or stem cell lineage development, favoring the generation of myeloid rather than lymphoid cells [116]. Contradictorily, a study discovered unaffected CD4 + T cell recovery in thymectomised mice compared to wild-type counterparts, calling into question the presumptions about thymic output [111]. In addition, glucocorticoids mediate apoptosis of double-positive cells through activation of the mitochondrial pathway, which may also be one of the mechanisms of infection-induced acute thymic degeneration [117].

The journey of bone marrow regeneration begins with hematopoietic stem cells (HSCs) in the bone marrow, first differentiating into lymphoid progenitors before evolving into T and B cells. Bone marrow lymphoid precursors play an essential role in lymphocyte recovery, as CLP surgery induces the proliferation of both long-term and short-term HSCs [118]. A plethora of apoptosis and immune suppression-associated proteins have been identified in the bone marrow of septic patients [37, 119–122]. Despite ceasing marrow cell apoptosis, B and T cell counts did not rebound [123], indicating a marrow "void". The pivotal role of G-CSF in CLP-induced osteoporosis, at least partly driving lymphopenia, has been emphasized [123]. The bone marrow is also the leading site of CD4 + memory T (Tm) cell homing and proliferation [122], and bone marrow CD4 + T cells have a higher basal proliferation rate than splenic T cells. One study highlights the significant post-sepsis expansion of the main CD4 + T cell subset (effective Tm cell) in the marrow, increasing from 51.2 to 66.3% at day 7 and 81.2% at day 14 post-CLP. Concurrently, secondary lymphoid organs like lymph nodes and spleen witnessed a decrease in memory phenotype T cells, with only effector T cells temporarily increasing [122], signifying the impact of sepsis on the regenerative ability of marrow lymphocytes, thereby influencing peripheral lymphocyte recovery. Another study has shown that the reduction in early T-lineage progenitor cell numbers in the thymus of septic mice is not a result of diminished bone marrow hematopoiesis but instead that reduced chemokine receptor expression leads to impaired bone marrow lymphoid progenitor cell homing capacity [116]. The reduction of initial lymphocytes in sepsis may also be related to osteoblast ablation [123], where bone loss induces a decrease in osteoblast-derived IL-7, leading to impaired early common lymphoid progenitor cell production, and parathyroid hormone stimulation of osteoblasts ameliorates sepsis-induced lymphopenia.

Peripheral naïve T cells following sepsis lymphopenia undergo homeostatic proliferation to compensate for cell loss and express memory signature markers (CD4: $CD44^{hi}$, $CD62L^{lo}$ [42]; CD8: $CD8\alpha^{lo}$, $CD44^{hi}$, $CD11a^{hi}$) [124]. Restoration of CD4 + T cell numbers is accompanied by the upregulation of antigen-activated markers CD11a and CD49d [111]. Although antigenic cross-reactivity cannot be ruled out, individuals may develop effector cell characteristics without specific antigenic stimulation [125]. Two pivotal studies sequentially established that antigen-specific phenotypic CD4 + T cells from non-septic backgrounds fail to expand via homeostatic proliferation post-adoption transfer to septic mice by day 14 [42]. In contrast, initial and transferred antigen-specific CD4 + T cells both proliferate on day 30 post-sepsis and gain antigen experience without specific antigen stimulation, denoting the occurrence of homeostatic (not antigen-stimulated) proliferation [111]. The former emphasizes the vital role of the in vivo microenvironment, while the latter highlights the intrinsic drive for homeostatic proliferation. Initial CD8 + T cells also undergo homeostatic proliferation and exhibit a similar effector/memory CD8 + T cell phenotype [126, 127], but the process requires assistance from CD4 + T cells.

Interestingly, homeostatic proliferation of CD4 + T cells may be inhibited by CD8 + T cells [42]. Besides, intestinal translocation of enteric-derived segmented filamentous bacteria in sepsis increases the number of antigen-specific CD4 + T-cells, suggesting that CD4 + T cells may also undergo antigen-driven proliferation and acquire a "memory-like" phenotype [128]. Recent findings illustrate that despite similar sepsis-induced damages to memory CD8 + T cells with varying stimulation histories, those with fewer stimulations exhibit more robust proliferative capabilities during recovery, altering the memory T cell pool composition [129]. In addition, telomere length in CD4 + T cells is shortened in individuals with sepsis. In contrast, no significant changes are observed in the CD8 + T cell population in terms of quantity, apoptosis rate, and telomere length in these patients [14].

Innate immune dysregulation

Inhibitory cytokines (e.g., IL-10 and TGF-β) following the onset of sepsis may alleviate the uncontrollable cytokine storm, but they inadvertently lead to a reduction in lymphocyte count. The decline of lymphocytes in various tested tissues (including spleen, mesenteric lymph

nodes, ileum, and colon) in a mouse model of sepsis corresponds with an increase in IL-10 and TGF-β [130]. In later stages of sepsis, splenic macrophages inhibit T lymphocyte proliferation through TGF-β production [131], while on the other hand, Tregs facilitate T lymphocyte apoptosis via TGF-β [76]. Notably, IL-6, a "double-edged sword" inflammatory cytokine, can reduce bone marrow lymphocytes by activating bone resorption. In contrast, anti-G-CSF neutralizing antibodies alleviate the loss of lymphocytes in the bone marrow [123].

Additionally, the downregulation of MHC-II molecule HLA-DR expression caused by sepsis implies impaired antigen presentation processes and a hindered capacity for lymphocyte activation and differentiation [77]. However, the recovery of HLA-DR might precede the restoration of lymphocyte counts, hinting that the revival of innate immune capabilities could facilitate lymphocyte recovery [77]. A significant decrease in the number of HLA-DR molecules on CD14 monocytes characterizes the immunoparalysis of sepsis. Overproduction of proinflammatory cytokines by monocytes/macrophages and dysregulation of lymphocytes characterized by CD4 lymphopenia and, subsequently, B-cell lymphopenia. Treatment with the IL-6 blocker Tocilizumab partially restored HLA-DR expression and increased absolute lymphocyte counts in COVID-19 patients [132].

Upregulation of inhibitory immune checkpoints

PD-1, CTLA-4, T cell immunoglobulin and mucin-domain containing-3 (TIM-3), lymphocyte activation gene-3 (LAG-3), and B and T lymphocyte attenuator (BTLA) are classical immune checkpoint receptors expressed on T cells, especially activated T cells [133]. Upregulated immune checkpoints in sepsis can lead to lymphopenia and proliferation disorders through various mechanisms [134]. When engaged by its ligand, programmed death-ligand 1 (PD-L1), PD-1 inhibits T cell proliferation, leading to T cell exhaustion and lymphopenia in sepsis [135]. PD-1-deficient T cells have a proliferative advantage over wild-type T cells during lymphopenia-induced proliferation, which is MHC-II dependent and independent of IL-7 [136]. Similarly, the upregulation of PD-L1 during sepsis contributes to the immunosuppressive state and lymphopenia [137]. CTLA-4 competes with CD28 for binding to CD80 and CD86 on antigen-presenting cells, inhibiting T-cell proliferation [138]. In sepsis, increased expression of CTLA-4 contributes to lymphopenia [135, 139, 140]. TIM-3 and LAG-3 negatively regulate T cell proliferation and accelerate T cell exhaustion or apoptosis, contributing to lymphopenia in sepsis [138, 141, 142]. BTLA-mediated suppression of T-cell responses could also contribute to lymphopenia [143, 144]. In sepsis, increased expression of BTLA on leukocytes has been associated with a higher risk of sepsis, subsequent infections, and more extended hospital stays. Moreover, a soluble form of BTLA is elevated in sepsis and is associated with disease severity and mortality [145].

The non-classical immune checkpoints CEACAM1 and TRAIL have been elevated in septic patients. CEACAM1 interacts with Src homology protein-1, suppressing the production and proliferation of IL-2 in human T cells and diminishing the expression of the IL-2 receptor [146, 147]. Through its induced apoptotic mechanisms, TRAIL reduces CD8 + T cell numbers [148]. In summary, upregulated immune checkpoints contribute to lymphopenia and proliferation disorders in sepsis by inhibiting T cell proliferation, promoting T cell exhaustion, and inducing T cell apoptosis.

Increased proportion of inhibitory cells

During the progression of sepsis, various immunosuppressive cells are abnormally activated and proliferate, leading to a widespread reduction in lymphocytes. Tregs play a crucial role in maintaining immunological homeostasis and preventing autoimmunity. This cell category witnesses a surge in its proportional representation, and it exerts inhibitory effects on the proliferation of effector T cells by releasing suppressive cytokines such as TGF-β and IL-10 [76, 149, 150]. In sepsis, the impairment in the differentiation and maturation of immature cells leads to their persistence as MDSCs, thereby causing a marked suppression in acquired immune responses [65]. This suppression is multifaceted, primarily involving the induction of T cell apoptosis through mechanisms such as the iNOS-mediated depletion of L-arginine and enhanced PD-L1 expression on MDSCs, culminating in lymphopenia [151].

Additionally, MDSCs contribute to sepsis-induced immunoparalysis, a state marked by damaged T cells, where they inhibit lymphocyte proliferation [65, 151]. The immunosuppressive properties of MDSCs are further elucidated through a range of mechanisms, including overproduction of Arginase 1 affecting T cell production [152, 153]. MDSCs also enhance the production of TGF-β and IL-10, thereby indirectly facilitating the expansion of Tregs. Moreover, the overexpression of PD-L1 on MDSCs interacts with the PD-1 receptor on T cells, potentially promoting differentiation towards Tregs. Additionally, the increased production of Fas ligand by MDSCs accelerates T cell apoptosis, while augmented activity of indoleamine 2,3-dioxygenase leads to L-tryptophan depletion, impeding T cell proliferation [65, 154].

Metabolism

The immune metabolism of T cells undergoes several notable alterations during sepsis, including reduced glucose transporter type 1 expression, decreased glucose uptake and proliferative capacity, markedly reduced baseline ATP levels, and decreased oxidative phosphorylation and glycolytic pathway activity [155]. The mammalian target of rapamycin activation functionality within T lymphocytes is also impaired [155]. Moreover, in bacterial sepsis patients, those with severe lymphocyte depletion exhibited lower triiodothyronine concentrations than those without lymphopenia [156]. In patients with COVID-19 sepsis, when contrasting those without lymphopenia against those with severe lymphopenia, the latter group displayed a significant drop in plasma levels of thyroid-stimulating hormone, thyroxine, free thyroxine, and triiodothyronine [156]. Thyroid hormones can foster cellular proliferation by binding with thyroid receptors, recruiting co-activators, and modulating gene transcription through thyroid response elements [157]. Additionally, thyroid hormones can regulate cellular proliferation through non-genomic mechanisms, such as activating the mitogen-activated protein kinases and phosphoinositide 3-kinase pathways [158]. However, the intricate mechanisms by which thyroid hormones impact T-cell proliferation during sepsis remain elusive and necessitate further research.

Heterogeneity

Aging is correlated with alterations in lymphocytes. In older individuals severely affected by sepsis, a pronounced decrease in lymphocytes, especially in T cells, is evident, with these reductions persisting over extended periods [40, 62]. In a study involving 2300 sepsis patients, 42.6% demonstrated enduring lymphopenia, primarily observed in elderly individuals who also presented a higher prevalence of chronic complications and elevated APACHE IV and SOFA scores [56]. Further, elderly sepsis patients manifested exacerbated apoptosis and proliferative disturbances in CD4 + T cell subsets [159]. Aging and nutritional changes could augment the effects of cellular apoptosis [160]. Additionally, diminished TCR diversity, spurred by lymphopenia, aggravates immune aging, potentially escalating the readmission rates in elderly patients. Remarkably, similar trends of persistent lymphopenia and raised regulatory T cell frequencies have been noticed not only in the elderly but also in neonates with hospital-acquired sepsis and early clinical infections [41, 161].

Different pathogens may induce diverse lymphopenic patterns. Numerous studies distinctively addressing bacterial and viral-induced sepsis have yielded results beneficial for precision therapy. Gram-positive and Gram-negative bacterial infections can reduce B/T cells, albeit more pronounced in the former case [162–164]. Prolonged lymphopenia was significantly associated with worse clinical prognoses in influenza and SARS-CoV-2 infections but not other respiratory viruses [165]. Moreover, extensive replication of the SARS-CoV-2 virus is conjectured to be a plausible cause of lymphopenia in COVID-19 patients, as high viral loads might diminish peripheral blood lymphocyte counts either by inducing more significant cell apoptosis or by prompting lymphocyte migration to infected tissues [166]. The research also indicated a positive correlation between C-reactive protein (CRP) and ferritin levels with viral load and a negative correlation with lymphocyte count, suggesting that control of viral replication could ameliorate lymphopenia [166]. This hints at the necessity of considering tissue infiltration effects in lymphocyte count evaluations and proposes the potential utility of CRP and ferritin as readily accessible clinical indicators to reflect the correlation between lymphocyte levels and specific viral loads. Research also highlights that host genetic variations might affect lymphocyte quantities [167]. A broader discussion encompassing more heterogeneous evidence is underway.

Redistribution of activated cells

The development and colonization processes of lymphocytes have been reviewed extensively in other studies [11, 168]. In patients in infection settings and ICU, there is a noted decrease in the quantities of T cells and NK cells compared to healthy control groups, a phenomenon potentially attributable to the migration of these cells to sites of infection or organ damage or peripheral lymphoid tissues during the immune response [169, 170]. When lymphocyte counts fall below 1,000/μL, it may be related to lymphocyte migration or isolation at specific locales [66, 171]. Studies conducted on healthy rhesus monkeys have indicated that post the initial dose of IL-7 treatment, there is a transient reduction in T cells, owing to the entry of lymphocytes into various tissues, including the intestines, skin, and lymph nodes [28, 172, 173]. This decrease is influenced by the upregulation of chemokines and adhesion molecules on CD4 + T cells and CD8 + T cells. These discoveries support the activated cell redistribution theory and elucidate, to some extent, the physiological mechanisms underlying lymphopenia. Notably, fluctuations in the quantity of NKT cells, a sub-group of T cells, post-sepsis are associated with the original site of infection, with redistribution generally occurring around 20 h post-surgery [174, 175]. Furthermore, in the early stages post-infection, there is a decline in the number of circulating mucosal-associated invariant T lymphocytes [176] or intestinal intraepithelial lymphocytes within

Table 3 Mechanisms of sepsis-induced lymphopenia

Mechanism	Observations	References
Lymphocyte apoptosis	The Fas/FasL signaling pathway mediates lymphocyte apoptosis in septic organ tissues.	[86, 87]
	Splenic T cells from nonsurvivors of sepsis show positive expression of cleaved caspase-9.	[18]
	Bcl-2 proteins block apoptosis in thymic and splenic T cells by inhibiting the mitochondrial pathway.	[35]
	Up-regulation of pro-apoptotic genes (including Bim, Bid, and Bak) and down-regulation of the anti-apoptotic gene Bcl-2.	[82]
	CHOP is upregulated and drives splenocyte apoptosis.	[83]
	STING leads to apoptosis by triggering ERS in splenic T cells.	[95]
Supplementary obstacle	A decrease in the relative number of CD31 + thymus emigrating cells in the peripheral blood of septic mice confirms reduced thymic output.	[14]
	Sepsis results in poor homing of lymphoid progenitor cells from the bone marrow to the thymus or stem cell lineage development biased towards the generation of myeloid rather than lymphoid cells.	[116]
	A decrease in initial lymphocytes in sepsis is associated with osteoclast ablation.	[123]
	Peripheral naïve T cells following sepsis lymphopenia undergo homeostatic proliferation.	[124]
	Intestinal CD4 + T cells in sepsis patients also undergo antigen-driven proliferation and acquire a "memory-like" phenotype.	[128]
Innate immune dysregulation	The decrease of lymphocytes in the tissues of septic mice corresponds to an increase in IL-10 and TGF-β.	[130]
	Splenic macrophages inhibit T lymphocyte proliferation through TGF-β production.	[131]
	Tregs facilitate T lymphocyte apoptosis via TGF-β.	[76]
	IL-6 reduces bone marrow lymphocytes by activating bone resorption.	[123]
	Downregulation of HLA-DR expression due to sepsis affects lymphocyte activation.	[77]
Upregulation of immune checkpoints	PD-1 inhibits T cell activation and proliferation, leading to T cell exhaustion and lymphopenia in sepsis.	[135]
	Upregulation of PD-L1 during sepsis contributes to lymphopenia.	[137]
	CTLA-4 competes with CD28 for binding to CD80/CD86 on antigen-presenting cells, inhibiting T-cell proliferation.	[138]
	TIM-3 and LAG-3 negatively regulate T cell proliferation and accelerate T cell apoptosis in sepsis.	[138, 141, 142]
	Suppression of T-cell responses mediated by BTLA upregulation in sepsis leads to lymphopenia.	[143, 144]
	CEACAM1 inhibits IL-2 production and reduces IL-2 receptor expression in human T cells.	[146, 147]
	TRAIL decreases CD8 + T cell numbers by inducing apoptotic mechanisms.	[148]
Increased proportion of inhibitory cells	Tregs exert an inhibitory effect on the proliferation of effector T cells by releasing inhibitory cytokines such as TGF-β and IL-10.	[149, 150]
	Induction of T cell apoptosis through enhanced PD-L1 expression on MDSCs.	[151]
	MDSCs lead to the overproduction of arginase 1, which affects T-cell production.	[152, 153]
	Increased Fas ligand production by MDSCs accelerates T cell apoptosis, whereas augmented indoleamine 2,3- dioxygenase activity leads to L-tryptophan depletion, which hinders T cell proliferation.	[154]
Metabolism	Sepsis reduces glucose transporter type 1 expression, glucose uptake capacity, baseline ATP levels, oxidative phosphorylation and glycolytic pathway activity in T-cells.	[155]
	The mammalian target of rapamycin activation in T-cells is impaired.	[155]
	In patients with COVID-19 sepsis, plasma levels of thyroid-stimulating hormone, thyroxine, free thyroxine, and triiodothyronine are significantly decreased in lymphopenic patients.	[156]
Heterogeneity	Persistent lymphopenia is more pronounced in elderly patients with sepsis.	[40]
	Gram-negative bacteria can lead to more pronounced B/T cell reduction than Gram-negative bacterial infections.	[162–164]
	High SARS-CoV-2 viral loads reduce peripheral blood lymphocyte numbers by inducing more apoptosis or lymphocyte migration to infected tissues.	[166]

Table 3 (continued)

Mechanism	Observations	References
Redistribution of activated cells	The development of lymphopenia in patients in infected settings or ICU is associated with lymphocyte migration or isolation at specific sites.	[66, 169–171]
	After an initial dose of IL-7, a transient decrease in peripheral T-cells occurs due to the entry of lymphocytes into various tissues, including the intestines, skin, and lymph nodes.	[28, 172]

the small intestine CLP post-surgery [177]. These alterations do not negate the potential concurrent influence of cell apoptosis and localized redistribution resulting from infection. The above-known mechanisms of sepsis-induced lymphopenia are summarized in Table 3.

Advances in therapeutic research

It has long been acknowledged that early circulating lymphocyte apoptosis is tightly correlated with adverse outcomes in human septic shock [38]. Targeted inhibition of lymphocyte apoptosis can also improve the prognosis in animal models of sepsis. For instance, strategies such as Bim siRNA, caspase inhibitors, cell-penetrating peptides, and protein inhibitors can effectively reduce lymphocyte apoptosis and enhance survival rates in septic mice [178–181]. Theoretically, inhibiting lymphocyte apoptosis should be the most direct approach to reversing early lymphopenia in sepsis, yet there remains a lack of efficient and safe means to prevent apoptosis. A significant hindrance is that apoptosis inhibition might lead to the overactivation of innate immune cells and T cells [182], potentially resulting in uncontrollable cell proliferation and neutrophil accumulation in tissues, further inducing organ damage [183]. Noteworthy is that therapeutic cysteine protease inhibitors did not improve survival rates in septic mice with lymphocyte deficiency, highlighting that the presence of lymphocytes is a prerequisite for their efficacy [36, 179]. Consequently, addressing the issue of lymphocyte recovery post-loss has become a focal point of research [9, 28, 42, 184]. Like apoptosis inhibitors, candidate drugs aiming to enhance lymphocyte proliferative capacity, such as IL-7, have demonstrated potential in rescuing lymphocyte quantities and have achieved promising research advancements.

IL-7

Studies have shown a decline in IL-7 levels among sepsis patients and underscored IL-7's pivotal role in thymic occurrence and the survival and modest proliferation of peripheral naïve T cells [14, 123, 185]. IL-7 therapy has garnered considerable attention within the medical community, mainly due to its efficacy in restoring lymphocyte count and function [186, 187].

IL-7 treatment significantly elevates the number of CD3 + T cells in the spleen and lymph nodes post-sepsis induction [112]. Recombinant human IL-7 (rhIL-7) contributes to preserving CD4 and CD8 T cell subgroups within the mesenteric lymph nodes. A randomized controlled trial (RCT) highlighted that IL-7 induced the proliferation of CD4 + and CD8 + T cells and enhanced the expression of cell cycle marker Ki67 [28]. In patients with sepsis and severe COVID-19, IL-7 therapy resulted in lymphocyte counts that exceeded twice that of the control group [155]. Notably, initial IL-7 treatment may result in a transient decrease in CD8 + T cells, yet there is a subsequent substantial increase in lymphocyte count [112]. This temporary decline, statistically significant when compared to the placebo group, may correlate with the upregulation of lymphocyte surface adhesion molecules and chemokines, such as CXCR4, CCR7, α4β7, LFA-1, and VLA-4, facilitating T cell migration to infection sites [28]. Another RCT involving 40 septic patients unveiled that IL-7 might reverse lymphopenia by two mechanisms, including increasing Bcl-2 to prevent apoptosis and activating the PI3 kinase pathway to promote proliferation [29].

IL-7 can rectify the immunometabolic dysregulation of T lymphocytes in patients with septic shock by activating mTOR [155]. Ex-vivo rhIL-7 treatment can also amplify the functionality of T cells in COVID-19 patients exhibiting reduced lymphocyte counts [188]. Furthermore, human IL-7-Fc delivered via the non-replicative Modified Vaccinia virus Ankara can increase the proportion of naïve T cells in immunosenescent patients and reduce the proportion of effector memory T cells through STAT1 and STAT5 signal transduction [189]. In summary, as an immunotherapeutic agent, IL-7 has immense potential to restore lymphocyte numbers in sepsis patients and animal models. However, optimal therapeutic strategies and long-term effects of IL-7 in sepsis treatment remain to be further investigated.

Immune checkpoint inhibitors

Numerous studies suggest antibodies targeting immune checkpoints have exhibited positive immune-modulating effects in sepsis models and clinical trials. For instance, anti-PD-1 and anti-PD-L1 antibodies can reduce T lymphocyte apoptosis [119, 139, 190, 191]. Anti-BTLA [143, 192], anti-CTLA-4 [139, 140], and anti-2B4 antibodies [193] also decelerate the T lymphocyte apoptosis process

via distinct pathways. Nevertheless, therapy still confronts specific challenges. For example, while the anti-PD-1 antibody Nivolumab and the anti-PD-L1 antibody BMS-936559 have effectively ameliorated lymphocyte apoptosis with good tolerability, the lymphocyte count has not significantly altered [60]. This poses a substantial challenge for therapeutic strategies aimed solely at boosting lymphocyte numbers by inhibiting apoptosis.

β-adrenergic blockers

Sepsis is also characterized by autonomic dysfunction and elevated plasma levels of norepinephrine and epinephrine [44, 98]. While the stress response benefits the organism during the initial stages of injury, prolonged adrenergic stress might induce damage, compromising organ function [194]. Preliminary in vitro studies have shown that catecholamines can induce lymphocyte apoptosis within 24–48 h, and the β-blocker propranolol can partially inhibit this apoptotic effect [99]. β-adrenergic blockers can ameliorate immune suppression in septic mice, such as enhancing spleen CD4 + T lymphocyte counts, diminishing the proportion of regulatory T lymphocytes, and preserving the proliferative capacity of CD4 + T lymphocytes [195, 196]. As sepsis severity escalates, the splenic CD4 + T lymphocyte count decreases dose-dependently. However, the β-blocker esmolol can partially counteract this effect [195]. Esmolol can prevent the decline in the splenic CD4 + T lymphocyte ratio caused by sepsis and foster its proliferation, potentially by inhibiting the activity of regulatory T lymphocytes (CD25high CD127low) [196].

In contrast, β1-adrenergic agonists amplify the immunosuppressive functions of regulatory T lymphocytes. Beyond enhancing lymphocyte counts in septic mice, β-blockers attenuate systemic inflammatory responses and improve cardiac function [196]. Therefore, the role of β-blockers in sepsis treatment transcends merely enhancing hemodynamics; they also assist in adjusting lymphocyte counts. Notably, their usage in the early stages of septic shock remains contentious, with recommendations to administer them 12 h post-initiation of vasopressor therapy [197]. While this might be slightly late for preventing rapid lymphocyte apoptosis, it still holds therapeutic value for patients with cardiac dysfunction and sustained lymphopenia.

miRNAs

Prolific studies indicate that miRNA holds the potential to modulate pivotal pathways governing lymphocyte apoptosis and proliferation, thereby influencing the lymphocyte depletion caused by sepsis. miR-126 weakens the activation of the caspase signaling pathway, thereby attenuating lymphocyte apoptosis induced in septic rats [198]. Expression of miR-223 is higher in the survivor septic patients than in the nonsurvivor patients, and the miR-223 expression also correlates negatively with the percentage of apoptosis in lymphocytes [199]. Besides, miR-223 enhances Jurkat T cell proliferation in vitro, and inhibition of miR-223 suppresses G1/S transition [199]. MiR-223 is a protective factor in sepsis by reducing lymphocyte apoptosis and promoting cell proliferation [199]. In addition, miR-21, miR-125, and hsa-miR-7-5p have all been reported to reduce sepsis-induced apoptosis in lymphocytes [200–202]. In summation, therapeutic strategies targeting these miRNAs may present novel avenues for ameliorating lymphopenia instigated by sepsis.

Others

Adrenomedullin may relieve sepsis-induced immunosuppression by directly promoting the proliferation of T and B-cell through ERK1/2 phosphorylation [203]. Genipin can mitigate immunosuppression, thereby reducing

Table 4 Therapeutic efficacy of COVID-19 immunotherapy for Lymphopenia

Interventions	Observations	References
rhIL-7	Treatment with rhIL-7 ex vivo significantly improves T cell proliferation and IFN-γ production in cells from COVID-19 patients.	[188]
rhG-CSF	Treatment of COVID-19 patients with lymphopenia and no comorbidities with rhG-CSF leads to rapid restoration of lymphocyte (especially CD8 + T-cell and NK-cell) counts and appears to reduce the frequency of patients progressing to critical illness or death.	[208]
TNF-α blockers, including infliximab or anti-TNF receptor 1 antibodies	In vitro TNF-α blockade strikingly rescued Spike-1-specific CD4 T-cell proliferation and abrogated Spike-1-specific activation-induced cell death in peripheral blood mononuclear cells from patients with severe COVID-19.	[209]
Degalactosylated bovine glycoprotein formulations MAF and M capsules	Both MAF and M capsules prevent depletion and accelerate recovery of absolute lymphocyte counts in COVID-19 patients.	[210]
PG2, a novel injectable botanical containing *Astragalus* polysaccharides	Administration of PG2 is beneficial to patients with moderate to severe COVID-19 and lymphopenia.	[211]

T-lymphocyte apoptosis in the late stages of sepsis [204]. Decoy receptor 3 can enhance the survival rate of mice with sepsis by suppressing lymphocyte apoptosis mediated through the Fas-FasL pathway [205]. TP064, a small molecule inhibitor of the chromatin regulator protein arginine methyltransferase 4, inhibits splenic lymphocyte death in a polymicrobial sepsis model and effectively promotes mice survival [206]. Administration of the chemical chaperone TUDCA contributes to maintaining lymphocyte homeostasis by preventing lymphocyte apoptosis for treating sepsis-induced lymphopenia in polymicrobial sepsis [207]. In addition, researchers have tried a variety of approaches, including rhIL-7, recombinant human granulocyte colony-stimulating factor (rhG-CSF), TNF-α blockers, degalactosylated bovine glycoprotein formulations, and PG2 to ameliorate COVID-19-associated lymphopenia (Table 4).

Summary of known therapeutic medications

Basic and clinical studies attempting to ameliorate sepsis-induced lymphopenia have revealed some areas for improvement despite certain valuable expectations. Immune checkpoint inhibitors have been shown to reduce lymphocyte apoptosis and increase cell proliferation in sepsis models. However, a clinical trial has [60] shown that although anti-PD-1 monoclonal antibodies can enhance T-lymphocyte function, the absolute increase in the number of lymphocytes is minimal [60]. The advantage of these inhibitors lies in their targeted actions and clear regulatory directions. However, they suffer from a limited scope of effect, struggling to reverse the absolute reduction in lymphocyte numbers. Beta-blockers like esmolol can increase the number of splenic lymphocytes and improve immunosuppression states in septic mice. However, the underlying mechanism remains unclear, probably maintaining lymphocyte numbers through indirect pathways [196]. However, their usage in early sepsis is constrained due to their traditional role in cardiovascular function regulation. MicroRNAs such as miR-126 and miR-223 can alleviate immunosuppression in sepsis by regulating apoptosis-related gene expression and affecting lymphocyte proliferation and apoptosis [198, 199]. This treatment strategy has the advantage of utilizing bioinformatics tools for high-throughput screening to identify efficient microRNA molecules. The downside is the existing issues of in vivo drug delivery and targeting specificity. IL-7 promotes the production of thymic and peripheral tissue lymphocytes [14], playing a crucial role in sustaining lymphocyte viability [186, 187], somewhat mitigating the shortcomings of immune checkpoint inhibitors. Administration of recombinant human IL-7 significantly boosts T-lymphocyte counts in the spleens and lymph nodes of sepsis animal models [112]. Clinical trials demonstrate that rhIL-7 treatment can swiftly restore peripheral blood lymphocyte numbers [28]. Its strengths include potent effects and effective restoration of the lymphocyte pool. However, it faces drawbacks such as a rapid drop in lymphocyte counts post single usage, necessitating multiple administrations, alongside undetermined safe dose ranges and long-term effects.

In summary, these research accomplishments have expanded our understanding of sepsis treatment modalities, especially strategies related to immune modulation. Despite some positive advancements, determining the optimal therapeutic approach still necessitates further research, encompassing the exploration of appropriate dosages, treatment timings, and potential combined uses with other therapies.

Conclusion and prospects

Lymphopenia is a prevalent phenomenon during the progression of sepsis. It serves as an index for assessing the severity and prognosis of sepsis associated with a heightened risk of secondary infections [4, 6]. Numerous epidemiological studies have subsequently affirmed the direct correlation between peripheral lymphopenia and increased ICU admissions and mortality rates, particularly emphasizing the substantial decrease in T-lymphocytes [6, 61]. These findings catalyzed an extensive exploration of the cellular and molecular mechanisms underlying sepsis-induced lymphopenia in hopes of illuminating potential therapeutic avenues.

Current studies have preliminarily elucidated several underlying potential mechanisms, yet a deeper investigation into the dynamic changes and mutual regulation relationships of different stages and lymphocyte subgroups is imperative. The two underlying mechanisms of lymphopenia that can be generalized from the dynamics of lymphocyte reduction to recovery after sepsis are apoptosis and impaired proliferation. Apoptosis is thought to be the leading cause of the dramatic decrease in the absolute number of lymphocytes due to sepsis. In contrast, lymphocyte redistribution illuminates a relative decrease in lymphocyte count in the peripheral circulation [76, 169, 170]. Sepsis survivors tend to show signs of recovery of lymphocyte counts quickly, whereas nonsurvivors ultimately fail to recover lymphocyte counts [71]. Therefore, inadequate or untimely recovery of lymphocyte counts after sepsis is associated with poor outcomes, and the underlying factor affecting the recovery of lymphocyte numbers may be the relative lack of proliferative capacity [212].

From a therapeutic standpoint, comprehensive treatment strategies that restore lymphocyte quantity and function appear more promising. We anticipate the

development of more targeted, low-side-effect therapeutic drugs to prevent and rectify lymphopenia and immunosuppression induced by sepsis. We also foresee advancements in auxiliary diagnostic technologies, including establishing monitoring and early warning systems based on lymphocyte count and subgroups. It is essential to note the substantial heterogeneity in the degrees of lymphopenia among different patients, closely correlated with factors such as age, underlying diseases, and infection pathways. For instance, elderly sepsis patients experience more pronounced and persistent lymphopenia, a phenomenon associated with accelerated immunosenescence [40, 62]. Distinct pathogens induce varying patterns of lymphocyte decline [162–164], necessitating the differentiation of lymphocyte kinetic alterations in different types of sepsis patients to adopt more personalized treatment strategies. This area remains relatively unexplored and warrants further study

We hypothesize that the "immunosenescence phenomenon" induced by sepsis-related lymphopenia might explain the dynamic changes in lymphocyte numbers, describing a series of intrinsic processes from cellular reduction to proliferation impediments. T-cell aging is a primary contributor to immune suppression in the body, characterized by a series of phenomena, including thymic atrophy, reduced diversity of TCR, mitochondrial dysfunction, naïve -memory imbalance, and weakened cell proliferative capacity [213]. These phenomena are witnessed not only in septic patients with lymphopenia who succumbed to the disease but also in younger lymphopenic survivors who have not reached senescence. Studies have illustrated that physiological stress can induce peripheral T-cell aging [214]. During severe sepsis, the organism endures accumulated physiological stress involving the hypothalamic-pituitary-thyroid axis, sympathetic nervous, and cardiovascular systems [215]. It is noteworthy that sepsis is a critical illness with acute onset, where pathological factors can rapidly accumulate pathological stress. This situation amplifies the inflammatory response and may push the individual into a state of stress that significantly accelerates the immune senescence process, leading to a drastic reduction in lymphocyte numbers and proliferative impotence.

The contribution of physiological elements such as catecholamines to lymphopenia has been discussed previously, and the potential efficacy of β-adrenergic antagonists in restoring lymphocyte counts has also been highlighted [195, 196]. Furthermore, IL-7 has demonstrated positive effects in reversing bone marrow and thymic T-cell recovery [28, 29]. These strategies have been positively affirmed in alleviating T-cell senescence [189]. Consequently, we advocate considering the resolution of T-cell aging issues stemming from "accumulated pathological stress" in sepsis as a therapeutic bridge to address early lymphopenia and long-term immune suppression. In cases where strategies based on preventing lymphocyte apoptosis are ineffectual, halting the accumulation of physiological stress can serve as a potential treatment strategy and complement IL-7 proliferative therapy.

In conclusion, lymphopenia is considered a biomarker of sepsis-induced immunosuppression. It is necessary to draw the attention of clinicians to the lymphopenia (ALC < 1,000 cells/μL) observed in septic patients, especially persistent severe lymphopenia (ALC < 500 cells/μL), which is highly associated with secondary infections and death. However, there is currently no consensus on the timing and frequency of sampling of ALC detection, which requires particular attention in future large-scale studies. In terms of pharmacological treatment, rhIL-7 appears to be a promising option for the safe and rapid reversal of severe septic lymphopenia and maintaining ALC for up to several weeks after cessation of therapy. In addition, given that lymphopenia occurs immediately after sepsis, appropriate pharmacological interventions can generally be initiated within 48 h of the diagnosis of sepsis, i.e., after two ACL tests have confirmed lymphopenia.

Abbreviations

ALC	Absolute lymphocyte count
BTLA	B and T lymphocyte attenuator
CAP	Community-acquired pneumonia
CHOP	C/EBP homologous protein
CLP	Cecal ligation and puncture
CRP	C-reactive protein
ERS	Endoplasmic reticulum stress
HSCs	Hematopoietic stem cells
ICU	Intensive care unit
LAG-3	Lymphocyte activation gene-3
L-CAP	Lymphopenic community-acquired pneumonia
MDSCs	Myeloid-derived suppressor cells
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
RCT	Randomized controlled trial
rhG-CSF	Recombinant human granulocyte colony-stimulating factor
rhIL-7	Recombinant human IL-7
RICD	Reactivation-induced cell death
STING	Stimulator of interferon genes
TCR	T-cell receptors
TIM-3	Immunoglobulin and mucin-domain containing-3
Tm	Memory T
Tregs	Regulatory T cells
UPR	Unfolded protein response

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Author contributions
W-ZB and TY conceptualized; W-ZB and Z-WZ drafted the manuscript; LX and C-LL performed the literature collection and collation; TY and C-LL reviewed and revised the manuscript. All authors have approved the final vision of this manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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